UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,384	12/21/2000	Saverio Carl Falco	BB-1167-B	2363

23906 7590 12/30/2002

E I DU PONT DE NEMOURS AND COMPANY
LEGAL PATENT RECORDS CENTER
BARLEY MILL PLAZA 25/1128
4417 LANCASTER PIKE
WILMINGTON, DE 19805

EXAMINER	
BUI, PHUONG T	
ART UNIT	PAPER NUMBER
1638	15

DATE MAILED: 12/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/720,384	Falco et al.
Examiner	**Art Unit**
Phuong Bui	1638

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 15, 2002*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *12-19* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideratio

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *12-19* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examine

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *3,4*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Restriction election

1. The Office acknowledges the receipt of Applicant's restriction election filed October 15, 2002. Applicant elects Group I and SEQ ID NO:3 (or polynucleotide encoding SEQ ID NO:4) without traverse. Claims 12-19 are pending and are examined in the instant application. This restriction is made FINAL.

Sequence Listing

2. Applicant's CRF and paper sequence listing have been entered. However, upon examination of SEQ ID NO:3 and its corresponding amino acid sequence SEQ ID NO:4, it is unclear what region of SEQ ID NO:3 encodes SEQ ID NO:4. Clarification is required.

Information Disclosure Statement

3. Initialed and dated copies of Applicant's IDS form 1449 (filed February 26, 2001 and April 25, 2001) are attached to the instant Office action.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. See pages 5 and 15, for example.

Claim Rejections - 35 USC § 112, second paragraph

5. Claims 12-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 12, the first recitation of "APS" must be spelled out for clarification. Further, the Office interprets the "Clustal method of alignment" as using the default parameters set forth on page 5, lines 5-7.

In claim 12(b), it is suggested that "complement" be amended to full-length complement, since "complement" reads on a single base, which does not appear to be Applicant's intention.

In claims reciting "gene", gene implies a DNA sequence that exists in nature and includes coding and noncoding regions, as well as all regulatory sequences associated with expression. This does not appear to be Applicant's intention, as evidenced by Applicant's recitation of "chimeric gene". It is suggested that "A chimeric gene" be amended to "A recombinant DNA construct".

In claim 18, since no hybridization conditions are set forth, it is unclear under what stringency conditions hybridization is intended to occur.

In claim 18, it would appear that "sulfate assimilation protein" should be amended to "APS kinase" because the steps set forth is using a sequence which encodes APS kinase.

In claims 18-19, the metes and bounds of "a substantial portion" are unclear. It is suggested that the phrase be deleted.

Finally claims 13-18 are improperly dependent upon canceled claims 1 or 4. In order to expedite prosecution in this application, the Office is interpreting the dependency on "claim 1" to be --claim 12--, and the dependency on "claim 4" to be --claim 15--.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 101 Utility

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 12-19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either the asserted "APS kinase" utility or a well established utility. Before the utility of a sequence having *x*% sequence identity or a sequence obtained by screening a cDNA library can be addressed, the utility of the entire recited sequence, SEQ ID NO:3 encoding SEQ ID NO:4, must first be addressed. Applicant asserted that the nucleotide sequence SEQ ID NO:3 encoding SEQ ID NO:4 has the utility of coding for a polypeptide having APS kinase activity based upon sequence comparison with known sequences in the prior art. SEQ ID NO:3 was isolated from *Zea mays*. No region of SEQ ID NO:3 was shown to be essential for APS kinase activity. Applicant states that SEQ ID NO:3 appears to encode a polypeptide that is structurally related to the known APS kinase, SEQ ID NO:13, from *Catharanthus roseus* (Applicant's specification, pp. 16 and 17) and that "It may be possible to modulate the level of sulfur containing compounds in the cell, including the nutritionally critical amino acids cysteine and methionine." It is unclear how the presence of any polypeptide having sulfur assimilation activity can be identified based solely on structure alone, with the structural identity merely being over a primer length fragment of the polypeptide. The disclosed SEQ ID NO:3 is admitted to be an EST sequence which is not a complete open reading frame. While SEQ ID NO:3 is disclosed to encode a polypeptide, SEQ ID NO:4, having 52% identity to a known APS kinase of SEQ ID

NO:13, structural identity alone is not sufficient to establish an asserted utility. Applicant fails to teach the enzymatic domain or regions of the polypeptide essential for APS kinase activity. Without this information, it is not possible to determine whether the 52% structure in common between Applicant's SEQ ID NO:3 and the prior art SEQ ID NO:13 includes the enzymatic domain necessary for APS kinase activity. Based upon Applicant's disclosure, it is evident that extensive further research, not considered to be routine experimentation, would be required before one skilled in the art would know how to use the claimed invention. However, it has been established in the courts that a utility which requires or constitutes carrying out further research to identify or reasonably confirm a "real world" context of use is not a substantial utility.

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point--where specific benefit exists in currently available form--there is insufficient justification for permitting an applicant to engross what may prove to be a broad field." (*Brenner v. Manson*, 383 U.S. 519 (1966)).

Thus, while expression of an APS kinase would provide substantial benefit to the public, it is unclear how one of ordinary skill in the art would be able to use a nucleotide sequence encoding polypeptide having 52% structural identity to a known APS kinase to achieve a functional APS kinase without having to carrying out further research to identify or reasonably confirm APS kinase activity. In addressing claims drawn to nucleotide sequences encoding polypeptides having 80% sequence identity to SEQ ID NO:4, or a nucleotide sequence obtained through amplification from a cDNA library using a primer from SEQ ID NO:3, Lazar et al. (Molecular and Cellular Biology, March 1988, Vol. 8, No. 3, p. 1247-1252 (U)) teaches a

mutation of aspartic acid 47 and leucine 48 of a transforming growth factor α results in different biological activities (Title). Burgess et al. (The Journal of Cell Biology, 1990, Vol. 111, p. 2129-2138 (V)) teaches a single mutation at position 132 from lysine to a glutamic acid residue causes possible dissociation of the heparin-binding and mitogenic activities of heparin-binding (acidic fibroblast) growth factor-1 from its receptor-binding activities (Abstract). Broun et al. (Science, 13 November 1998, Vol. 282, p. 131-133 (W)) teaches as few as four amino acid substitutions can convert an oleate 12-desaturase to a hydroxylase and as few as six result in conversion of a hydroxylase to a desaturase (Abstract). The attached sequence search from GenEmbl shows the sequence results for various sequences having 100% local similarity over primer length regions of SEQ ID NO:3, none of which is disclosed as being an APS kinase. Note that at least six of the listed sequences are plant origin. Accordingly, absent guidance as to what region of SEQ ID NO:4 is critical for APS kinase activity, and given the lack of working examples of any such sequence having 80% sequence identity, Applicant has not provided sufficient evidence that the claimed sequences would have the asserted APS kinase activity. In addressing Applicant's use of sequence comparison solely to determine function, Bork (Genome Research, Vol. 10, 2000, p. 398-400 (X)) clearly teaches the pitfalls associated with comparative sequence analysis for predicting protein function because of known error margins for high-throughput computational methods. Bork specifically teaches that computational sequence analysis is far from perfect, despite the fact that sequencing itself is highly automated and accurate (p. 398, col. 1). One of the reasons for this inaccuracy is that the quality of data in public databases is still insufficient. This is particularly true for data relating to protein function. Protein function is context

dependent, and both molecular and cellular aspects must be considered (p. 398, col. 2). Conclusions from comparison analyses are often stretched with regard to protein products (p. 398, col. 3). Furthermore, although gene annotation via sequence database searches is already routine, even here the error rate is considerable (p. 399, col. 2). Most features predicted with an accuracy of greater than 70% are of structural nature and, at best, only indirectly imply certain functionality (see p. 399, Table 1 legend). In Table 4, Applicant indicated that SEQ ID NO:4 has 52% sequence identity to a known APS kinase protein, which is significantly less than Bork's 70%. As more sequences are added to databases and as errors accumulate and propagate, it becomes more difficult to infer correct function from the many possibilities revealed by a database search (p. 399, paragraph spanning cols. 2 and 3). Bork cautions that, although current methods seem to capture important features and define general trends, 30% of structure-function features are missing or predicted inaccurately. This must be kept in mind when processing the results (p. 400, paragraph spanning cols. 1 and 2). Thus, given the teachings of Lazar et al., Burgess et al., and Broun et al., and given the limitations and pitfalls of using computational sequence analysis, as taught by Bork, it is apparent the biological function of SEQ ID NO:4 cannot be accurately predicted, based upon sequence similarity with sequences of the prior art. Additionally, there also is no established utility for SEQ ID NO:3 and SEQ ID NO:4. Applicant should note that SEQ ID NO:3 does not have an established utility for hybridization purposes because the utility of the protein encoded by SEQ ID NO:3 has not been shown to be substantial as indicated above. Applicant should further note that a polynucleotide encoding SEQ ID NO:4, or a nucleic acid sequence obtained using a primer of SEQ ID NO:3, would not necessarily

hybridize to SEQ ID NO:3 due to codon degeneracy and the overall length of the nucleic acid sequence, respectively. Thus, for the reasons set forth, the claimed sequences do not have a real-world use and hence lack utility (see Utility Examination Guidelines published in Federal Register/ Vol. 66, No. 4/ Friday, January 5, 2001/ Notices; p. 1092-1099).

Claim Rejections - 35 USC § 112, first paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 12-19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either an "APS kinase" asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 12-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to an isolated polynucleotide comprising a nucleotide sequence encoding a polypeptide having at least 80% sequence identity to SEQ ID NO:4, and nucleic acid fragments obtained by probing and primers. First of all, the translated amino acid sequence SEQ ID NO:4 is only a partial sequence of a protein. SEQ ID NO:3, which encodes SEQ ID NO:4, is only a partial gene sequence and does not encode a complete open reading frame. Neither

Applicant's disclosure nor the state of the prior art provides guidance as to how one skilled in the art would be able to reliably predict the structure of the entire gene sequence or protein sequence based upon the disclosure of SEQ ID NO:3 and SEQ ID NO:4. The breadth of the claims reads upon complete gene sequences having in common a nucleotide sequence encoding SEQ ID NO:4, including mutants and allelic variants. There is insufficient relevant identifying characteristics to allow one skilled in the art to predictably determine the complete structure of a gene encoding a SEQ ID NO:4, or its mutants and allelic variants, absent further guidance. Since the claimed genus, i.e, SEQ ID NO:3 or the nucleotide sequence encoding SEQ ID NO:4, encompasses undisclosed genes or genes yet to be discovered, the disclosed structural feature does not constitute a substantial portion of the claimed genus. Therefore, the disclosure of SEQ ID NO:3, or the nucleotide sequence encoding SEQ ID NO:4, does not provide an adequate description of the claimed genus, and in view of the level of knowledge and skill in the art, one skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of DNAs which comprise the nucleotide sequence encoding SEQ ID NO:4 (see Written Description Requirement published in Federal Register/ Vol.66, No. 4/ Friday, January 5, 2001/ Notices; p. 1099-1111).

Secondly, the 80% sequence identity recitation in the claims may encompass APS kinases from other organisms and plants which Applicant has not adequately described and is not in possession of. The disclosure of SEQ ID NO:3 obtained from *Zea mays* is not representative of the genus of APS kinases obtained from other plants and organisms, and is not representative of allelic variants and mutant APS kinases of *Zea mays*. The court held that to adequately describe

a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Thus, there is lack of adequate description to inform a skilled artisan that applicant was in possession of the claimed invention, i.e., the genus of APS kinases having 80% sequence identity to SEQ ID NO:4, at the time of filing.

Thirdly, claims 18 and 19 are directed to nucleic acid fragments obtained using probes and primers. In claim 18, the isolated nucleic acid fragment of claim 1 is used to probe a cDNA or genomic library to obtain other sequences which encode "a substantial portion" of a sulfate assimilation protein. Applicant teaches that a wide variety of enzymes are involved in sulfur assimilation including high and low affinity sulfate transporter proteins, sulfate adenylyltransferase, APS kinase, APS reductase, sulfite reductase, and serine O-acetyltransferase. Neither Applicant nor the state of the prior art teaches that APS kinase from *Zea mays* (SEQ ID NO:3) has sufficient sequence identity with other sulfate-assimilation-protein-encoding sequences from *Zea mays* or other species, or with APS kinases from other species, to allow probing under unspecified hybridization conditions using degenerate DNA (sequence encoding SEQ ID NO:4) to obtain other sulfate assimilation proteins. Applicant does not disclose a single nucleic acid fragment obtained by these methods from other regions of the *Zea mays* genome or from other plants and organisms encoding a substantial portion of a sulfate assimilation protein (note that the claimed sequence does not require sulfate assimilation protein function). Absent of such disclosure, Applicant has not adequately described the structures of claimed nucleic acid

fragments having the sulfate assimilation protein function obtained by this method. In claim 19, the claimed nucleic acid fragment is obtained using an oligo primer of unspecified size from an unspecified region of SEQ ID NO:3 under unspecified hybridization conditions. Again, Applicant does not disclose a single nucleic acid fragment obtained by this method from other regions of the *Zea mays* genome or from other plants and organisms encoding a substantial portion of a sulfate assimilation protein. Thus, since Applicant is not in possession of any such sequence, and Applicant has not adequately described the structure of any sequences obtained by this method, the written description requirement is not met.

11. Claims 18-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In addition to lacking written description as discussed above, these claims are not enabled because in claim 18, using degenerate DNA under unspecified hybridization conditions would result in obtaining nucleic acid sequences most of which would have no known sulfur assimilation protein function. Further, it is unclear how one skilled in the art can use degenerate DNA encoding an APS kinase protein and obtain DNA sequences encoding sulfur assimilation proteins, since there are many other sulfur assimilation proteins in addition to APS kinase which have no known sequence homology to the APS kinase disclosed by Applicant (p. 1 of specification).

Claim 19 is not enabled because an oligo primer of unspecified size from an unspecified region of SEQ ID NO:3 not known to be unique to a sulfur assimilation protein encoding sequence would also result in obtaining nucleic acid fragments most of which would have no known sulfur assimilation protein function. Again, it is noted that SEQ ID NO:3 encodes an APS kinase of *Zea mays*, and thus would unlikely hybridize to other sulfur assimilation protein encoding sequences.

Accordingly, the claimed invention is not enabled.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 12-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Arz et al. (Biochimica et Biophysica Acta 1218 (1994), pp. 447-452, (cited in IDS, Paper No. 3, filed February 26, 2001), from which the Applicant's admitted prior art SEQ ID Nos: 13 and 14, NCBI Identifier Nos. g2832300 and g1076283, were obtained.

The scope of the claims encompasses sequences which are not the full-length complements of the nucleotide sequence encoding SEQ ID NO:4 (claim 12(b) reads on a single codon), and thus would encompass any nucleotide sequence encoding an APS kinase, or a sulfur assimilation protein. In addition, claims 18 and 19 are further broader in scope in that these claims cover any nucleic acid sequence encoding a sulfur assimilation protein and which shares a

primer length fragment with SEQ ID NO:3 or with the nucleic acid sequence encoding SEQ ID NO:4 or with any complement (of any length) of either of those sequences. Because of the breadth of these claims, it is clear that Applicant's admitted prior art SEQ ID Nos: 13 and 14 obtained from Arz et al. sufficiently match SEQ ID NO:4 so as to read on the claimed invention as presented. Accordingly, Arz et al. anticipated the claimed polynucleotide which is the complement of the nucleotide sequence encoding SEQ ID NO:4, as well as the "chimeric gene", transformed host cell, and nucleic acid fragments of claims 18-19.

With regard to claims 12-17, this rejection may be overcome by amending "complement" of claim 12(b) to read as --full-length complement--.

Remarks

11. No claim is allowed. SEQ ID NO:3 and a nucleotide sequence encoding SEQ ID NO:4 are free of the prior art.

12. Papers relating to this application may be submitted to Technology Sector 1 by facsimile transmission. Papers should be faxed to Crystal Mall 1, Art Unit 1638, using fax number (703) 308-4242. All Technology Sector 1 fax machines are available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Bui whose telephone number is (703) 305-1996. The Examiner can normally be reached Monday-Friday from 6:30 AM - 4:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Phuong Bui
Primary Examiner
Art Unit 1638
December 26, 2002

Phuong Bui 12/26/02
PHUONG T. BUI
PRIMARY EXAMINER